Building action repertoires: memory and learning functions of the basal ganglia

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Research on the basal ganglia suggests that they are critically involved in building up sequences of behavior into meaningful, goal-directed repertoires. Work on rodents, monkeys and humans suggests that the basal ganglia act as part of a distributed forebrain system that helps to encode such repertoires through behavioral learning, and that is engaged in the expression of such repertoires once they have been internalized. The basal ganglia also may be critical to the expression of innate behavioral routines. Experimental findings on reward-based learning suggest that neural activity in the striatum and substantia nigra, pars compacta changes during behavioral learning. New evidence also suggests extreme specificity in the neural connections interrelating the basal ganglia, cerebral cortex and thalamus. Adaptive control of behavior may centrally depend on these circuits and the evaluator–reinforcement circuits that modulate them.

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Introduction

A major shift is under way in work on the basal ganglia. After years of painstaking work to build up knowledge of the basic anatomy, neurochemistry and cell physiology of the system, studies are now increasingly being directed toward functional issues and toward testing hypotheses about basal ganglia function. At the same time, there is renewed emphasis on trying to understand the functions of the basal ganglia in terms of their interactions with the neocortex and other structures as parts of distributed neural circuits. This activity is attracting many new people to work on the basal ganglia, including computational scientists (see [1,2•,3•]). There is no consensus on 'the' function of the basal ganglia, but work with techniques ranging from imaging in humans to recording and chemical inactivation of basal ganglia sites in primates and rodents points to the basal ganglia as part of a highly dynamic neural system involved in adaptive control of action, not only in the motor sphere, but also at the level of planning and cognition.

The key functional theme that will be stressed here is that the basal ganglia are involved in one or more stages of the building up, storage, decoding, retrieval and expression of behavioral action plans through collaboration with the neocortex, the thalamus and the limbic system (Fig. 1). These functions, partly subsumed under such terms as procedural or skill learning, sequence learning or habit formation, were already emphasized explicitly by Hirsh [4], Van Den Bercken and Cools [5], Mishkin and Petrie [6], and Hikosaka and Wurtz [7] many years ago and have been suggested implicitly by studies indicating that the basal ganglia act in selecting or planning behaviors or motor acts processes dependent on plasticity, active memory, and retrieval, as well as forward planning. But what precisely do the basal ganglia contribute to these functions? What are the mechanisms involved? How do we take account of the regional specializations of the basal ganglia, whereby the component nuclei have districts primarily interconnected with motor, premotor, prefrontal or posterior association cortices? What are the functions of the several loop pathways that have been implicated in modulating basal ganglia? And why, if learning and memory are so central to basal ganglia function, have these not been emphasized, until recently, in the rich history of clinical work on the basal ganglia (see [8–11] and references therein)? These questions are at the forefront of the field.

Dorsal striatum is implicated in learning and memory in the rodent

Experimental psychologists have led the way in implicating the striatum in learning and memory functions

Abbreviations

GABA—γ-aminobutyric acid; **GPe**—globus pallidus, pars externa; **GPi**—globus pallidus, pars interna; **IPSP**—inhibitory postsynaptic potential; **M1**—primary motor cortex; **MPTP**—1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; **PET**—positron emission tomography; **SMA**—supplementary motor area; **SNr**—substantia nigra, pars reticulata; **TAN**—tonically active neuron.

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and in demonstrating dissociations between memory performance disrupted by lesions of the caudoputamen and those disturbed by lesions of the hippocampus and amygdaloid complex in rodents (e.g. [12–15] and references therein). Such work suggests that the caudoputamen is necessary for the formation of stimulus–response associations that are built up through reinforcement. It also indicates that different parts of the caudoputamen have different memory-related functions (for example, the medial part is involved in conditional reward tasks, whereas the lateral part functions in stimulus–response learning).

In two new studies that directly compare striatal-, hippocampal- and amygdala-based functions in rats performing in the Morris water maze, McDonald and White [16•] and Packard *et al.* [17•] used lesions and local amphetamine injections to depress or enhance functions in these sites and provided further evidence for a 'cue learning' (as opposed to hippocampal 'place learning') function for the caudoputamen. The amygdala contributes to both types of learning. Such studies are important as they refine the notions of multiple memory systems in the brain and emphasize that, even within the striatum, different regions may serve different aspects of mnemonic processing. One interesting interpretation of the response (cue) learning paradigm is that it reflects an egocentric navigational control system for movements in extrapersonal space, as opposed to the allocentric spatial relations system of the hippocampus (see [15,18–20]).

The dorsal striatum and the substantia nigra are implicated in reward-based learning in the monkey

Neurons in the striatum have highly context-dependent firing properties, suggesting that their response patterns have been built up through learning and memory. How is this achieved? A major emphasis of work on monkeys has been on reinforcement-based learning, encouraged by the continuing series of papers by Schultz and co-workers [21•,22•] indicating that the dopamine-containing neurons of the substantia nigra pars compacta, not only those of the ventral tegmental area, fire in relation to primary rewards and reward-conditioned stimuli. The earlier studies of Rolls *et al.* (e.g. [23]) pioneered this direction. Now, two new papers [24••,25••] have documented plasticity of neural firing in the tonically active neurons (TANs) of the striatum in monkeys learning a sensorimotor conditioning task. This population response of the TANs is maintained even when the behavioral response has become highly automatic, but is diminished if dopamine is depleted in one striatum by the injection of the neurotoxin MPTP [25••].

These studies, taken together with those of Schultz and co-workers, suggest a model [26••] in which dopaminergic nigral neurons are recruited by novel rewarding stimuli, and long-term procedural memories are built up that are expressed under conditions of modulatory control by striatal dopamine (Fig. 1a). Whether the learning actually occurs in the striatum itself or in, for example, cortical regions projecting to the striatum, is left open by these studies, as is the question of how the changes in TANs affect the phasically active neurons of the striatum. The authors suggest, however, that as learning occurs, TAN activity becomes temporally coordinated. The authors believe that such coherence could underlie periods of enhanced plasticity in the striatal circuits during behavioral learning, so that new behavioral routines could gradually be acquired [27••]. When the synchronization is lost by virtue of dopamine depletion, a coherent 'go signal' for action might be lost. This loss of a synchronizing cue from the basal ganglia has been suggested by Martin *et al.* [28•] to characterize patients with Parkinson's disease.

Evidence for basal ganglia activity in learning and memory in the human

Imaging studies designed to detect activation of the basal ganglia in subjects carrying out carefully designed behavioral tasks are now directly addressing the question of basal ganglia involvement in memory mechanisms in the humans. Many of the recent PET findings have been reviewed by Brooks [29•], who emphasizes optimization (see [30•]) and selection (see [31]) — rather than learning — functions for the striatum. However, new work is supporting earlier imaging studies (e.g. [32,33]) indicating that the human striatum may indeed be activated in relation to learning tasks, procedural tasks requiring retrieval of procedural memory stores, and imagined movement and mental rehearsal of behavior [34•,35•].

Notable among the new studies are those by Jueptner and colleagues (M Jueptner *et al.*, unpublished data; M Jueptner, CD Frith, DJ Brooks, RSJ Frackowiak, RE Passingham, unpublished data; M Jueptner, CD Frith, RSJ Frackowiak, DJ Brooks, RE Passingham, unpublished data), following up on work by Jenkins *et al.* [36••] in which subjects carried out sequential button-press tasks. Jueptner and co-workers (M Jueptner *et al.*, unpublished data; M Jueptner, CD Frith, DJ Brooks, RSJ Frackowiak, RE Passingham, unpublished data; M Jueptner, CD Frith, RSJ Frackowiak, DJ Brooks, RE Passingham, unpublished data) make a strong case that the human striatum is differentially active during the learning of new, as opposed to familiar or repetitive, sequences of button-presses. Moreover, they demonstrated that the differential activation of the striatum during such new learning occurs preferentially in the anterior striatum (head of the caudate nucleus), and that the anterior putamen along with the caudate nucleus is activated in a free selection task requiring preparation

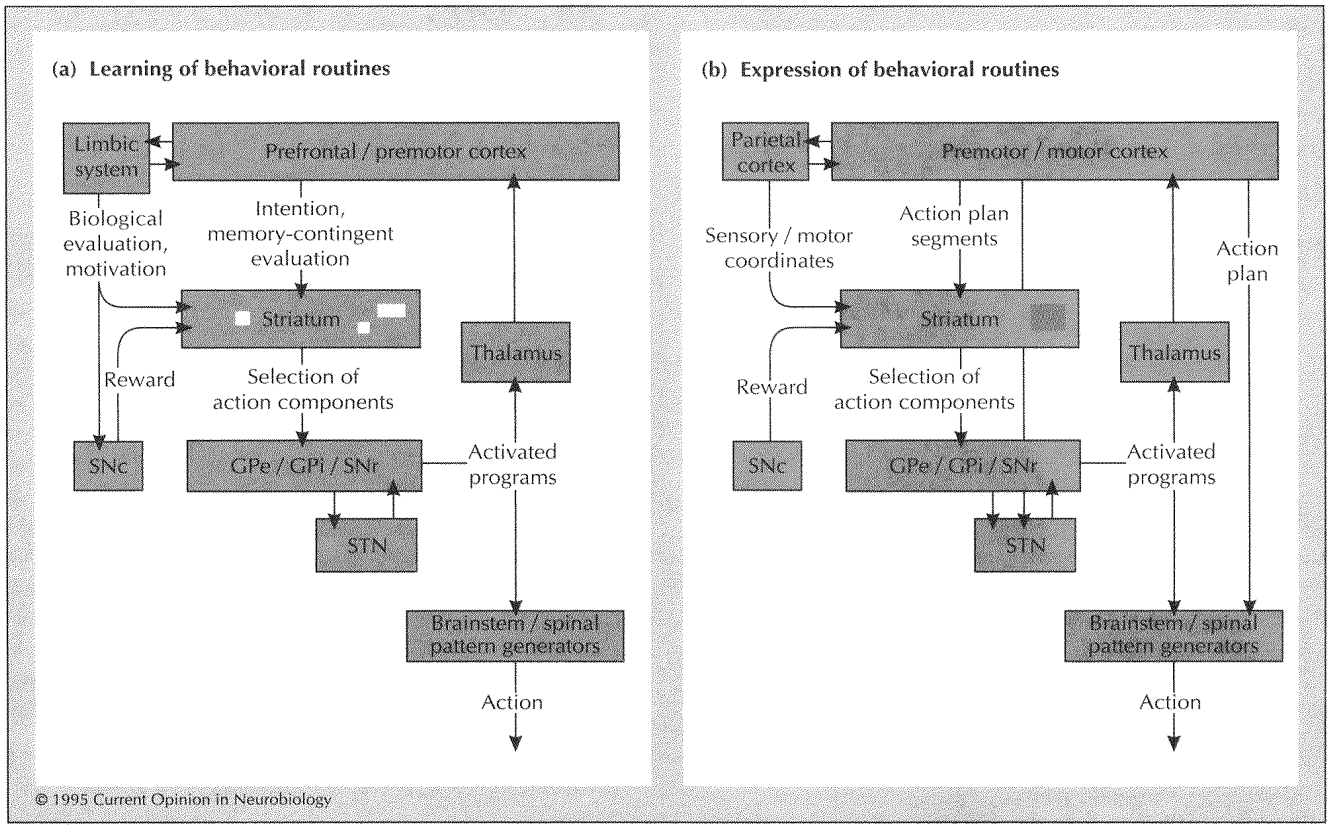

Fig. 1. Cortical and basal ganglia circuits collaborate in learning and memory functions. **(a)** Working model of how the basal ganglia may participate in the internalization of action plans during learning by experience. Cognitive information regarding intention and representations stored in working memory is processed in the prefrontal and anterior premotor cortices, both of which project strongly to the striatum, especially the caudate nucleus. These inputs are reconfigured in the striatum in relation to evaluative inputs about the significance of internal and external states, derived from the limbic system and substantia nigra pars compacta (SNc). As a result, particular action components are selected for potential activation. Processing through pallidonigral–subthalamic circuitry leads to differential activation of selected programs, which are forwarded to the cerebral cortex and to pattern generators in the brainstem and spinal cord. Over time, this system builds up behavioral routines. Parts of the system may run instinctual programs as well. Only a subset of basal ganglia pathways are shown. Pale squares indicate striosomes in the striatum (especially prominent in caudate nucleus). STN, subthalamic nucleus. **(b)** Working model of how basal ganglia may contribute to control performance of behavioral sequences. Inputs from premotor and motor cortex carrying information about action plans and inputs from parietal cortex adding sensorimotor spatial information are processed in the striatum (putamen and parts of the caudate nucleus). As in (a), activation of selected action programs, with suppression of others, occurs through pallidonigral–subthalamic circuitry. These activated programs are sent to the cerebral cortex, where they may serve as predictive controllers, and are forwarded to pattern generators in the brainstem and spinal cord. This system interacts with the learning system shown in (a), and is seen as modifiable and contingent on evaluation signals such as those from the SNc. Only a subset of basal ganglia pathways are shown. The dark square in the striatum symbolizes matrisomal organization of the putamen and caudate nucleus.

and decision, but not learning. By contrast, the caudate nucleus is not differentially active, as subjects carry out pre-learned or repetitive tasks. Instead, the main activation is in more posterior striatal regions, including the putamen. This topography may account for the differences in motor learning versus motor control deficits reported in Parkinson's patients [9]. There is a remarkable concurrence between this anteroposterior topography in the human striatum and that found by Hikosaka and colleagues (S Miyachi, K Miyashita, Z Karadi, O Hikosaka, abstract, Fifth International Triennial Meeting of the International Basal Ganglia Society, Nemuno-Sato, Japan, May 1995, page 57) in brain lesion studies with macaque monkeys carrying out sequential button-press tasks. Jueptner and colleagues (M Jueptner, CD Frith, RSJ Frackowiak, DJ Brooks, RE Passingham, unpublished data) make the further point that there is a general anteroposterior topography governing planning and executive functions in the frontal cortical–basal ganglia system as a whole. Figure 1 reflects this ordering.

The basal ganglia and planning ahead: neural representations of action sequences

A key paper on the supplementary motor area (SMA) by Tanji and Shima [37••] presents evidence that neurons in this cortical area fire selectively in relation to sequences of movements carried out in a particular order. This selectivity for the serial order of movements was not shown by neurons in the primary motor

cortex (M1) recorded under the same conditions in the same monkeys. For neuroscientists working on the basal ganglia, this is an exciting result. The SMA is a prime cortical target of the pallido-thalamo-cortical projection system.

There is growing evidence that the striatum itself is a structure critical for the representation of serial order of both learned and innate movement sequences. Early and continuing work on this issue has been carried out in rodents (see [38,39] and references therein). Evidence from lesion and recording experiments suggests that in rat 'syntactic grooming' sequences are encoded in the anterior caudoputamen. In an important new paper, Kermadi and Joseph [40••] document a strong representation of sequence information in the caudate nucleus of the macaque monkey. They demonstrate that not only movement-related activity, but also sensory (target)-related activity can be sequence specific. Interestingly, both Kermadi, Joseph and co-workers [40••,41] and Kimura [42] note that in tasks involving a sequence of movements, neurons in the caudate nucleus and the putamen can fire 100 milliseconds or more before the onset of electromyographic (EMG) activity in the prime mover muscles, a finding that stands in contrast to the relatively late firing of neurons tested with non-sequential tasks ([43]; see also [44]). Thus, the idea that the basal ganglia cannot be involved in the initiation of movement because their neurons are late-firing appears not to hold for all types of movement.

It is of the greatest interest that in neurologic disorders such as obsessive–compulsive disorder (in which perseverative sequences of behavior occur in the afflicted patients), abnormal metabolic activity is present in the anterior striatum as well as in frontal and anterior cingulate areas of the neocortex [45,46]. Indirect but consistent evidence from clinical studies of patients with Parkinson's disease also suggests that the striatum — and its dopamine-containing inputs from the substantia nigra — are important for performance of sequential behaviors and for predictive control [28•,47–52]. These clinical observations reinforce the notion that the basal ganglia and associated frontal cortical regions may allow the forward planning on which coordinated behavioral action sequences depend. It still is too early to integrate these findings with the large body of information about the ventral/limbic part of basal ganglia circuitry, but new studies suggest that this may soon be possible (see e.g. [53•,54•]).

Space–time coordination and behavioral sequence formation

The organization of behavior sequences, whether learned or innate, may critically depend on neural processing in the striatum, which not only receives massive cortical inputs relevant to sequence generation, but is also in a position to act on the cortex and on pattern generators in the brainstem [55] (Fig. 1). But what is the nature of sequence-related neural processing in the striatum, and how does it differ from and functionally integrate with sequence-related processing in the SMA and other cortical areas? These are open issues. Two recent models [26••,27••], however, do raise timing as a critical feature of neural processing in the striatum.

First, evidence suggests that many different cortical inputs need to converge on individual striatal projection neurons to bring these spiny neurons to firing threshold [56], and, further, that cortical inputs to these neurons are re-mapped systematically into convergent or divergent modules [57,58,59•,60•]. This sets up a situation in which the striatal projection neurons could act as modifiable coherence-detection elements [27••,58,59•,60•]: the hard-wired patterns of convergence of their cortical (or other) inputs may thus represent a template for neural processing, but activity-dependent temporal coordination of the inputs may determine their spike activity and hence striatal output activity.

Second, there are several sets of striatal interneuron that could act differentially to modulate the spatiotemporal dynamics of striatal input–output processing. One set, the cholinergic interneurons, is thought to correspond to the TANs, whose firing can be modified during behavioral learning. It has been suggested that these interneurons could serve a 'motor-binding' function, bringing about new patterns of temporal coherence in striatal output networks as a result of learning [26••,27••]. Another set of striatal interneurons, GABAergic neurons expressing parvalbumin, may be particularly sensitive to cortical inputs and are thought to be electrotonically coupled [61]. These, too, could help set up dynamic, modifiable activity states in striatal neurons that could influence the temporal order of striatal outputs. Simultaneous *in vivo* recording from multiple striatal neurons [62•] and *in vitro* studies of striatal neurons (e.g. [63,64]) will be valuable in addressing these issues. Of particular interest is evidence that local, fast collateral inhibition by spiny neurons may not occur in the striatum [65••], but that neuropeptides may be intrinsic slow messengers providing local modulation (T Aosaki, abstract, Fifth International Triennial Meeting of the International Basal Ganglia Society, Nemuno-Sato, Japan, May 1995, page 2).

Pendulum swings and controversies in basal ganglia circuit analysis

Work on the basic anatomy and physiology of the basal ganglia has been anything but dull. Issues related to the circuit functions include the following: identifying the cortical areas that receive the basal ganglia output; the

'parallel loop' nature of corticobasal ganglia circuits; the direct–indirect pathway model for basal ganglia anatomy; and, finally, the functions of striatal compartments.

What cortical areas receive the output of the basal ganglia? There is a growing view that much of the frontal cortex, and even part of the temporal cortex, receives basal ganglia output either by way of the pallidum or via the substantia nigra, pars reticulata (SNr), or through both routes ([66•,67•]; PL Strick, personal communication). According to a new study by Inase and Tanji [68•], even the 'motor pallidum' projects mainly to thalamic regions that do not project to M1, but, rather, to cortical regions involved in higher order aspects of motor control than those carried out by the M1. This view, in turn, suggests that the basal ganglia may primarily act in the 'selection'/'forward planning'/'active memory' roles of these cortical areas.

To what degree are corticobasal ganglia circuits parallel loops? The circuit anatomy of the basal ganglia clearly shows that the cortex and basal ganglia are interlinked (Fig. 1), but it is still a matter of debate whether there are separate circuits ('loops') for different cortical regions (e.g. for motor, supplementary motor, or lateral prefrontal cortex) [69], or an intermixing of the circuits. One of the best examples of circuit specificity involving basal ganglia connections is the pathway related to oculomotor control (the oculomotor loop), and Kori, Kata, Miyashita and colleagues [70•–72•] have now added further evidence for selectivity in this system. However, if the M1-recipient striatopallidal path leads mainly to non-M1 cortex, as suggested by Inase and Tanji [68•], parallelism of the loops cannot be absolute. Such cross-loop interactions are also suggested by Inase *et al.* (M Inase, ST Sakai, J Tanji, abstract, Fifth International Triennial Meeting of the International Basal Ganglia Society, Nemuno-Sato, Japan, May 1995, page 38) in their report documenting considerable overlap of M1 and SMA inputs to the macaque putamen. Joel and Weiner [67•] further suggest that the parallel loop model fails to take into account open 'split' circuits in the system, by which prefrontal cortex as well as premotor cortical circuits are engaged by the basal ganglia. Finally, interactions within nuclei in the basal ganglia circuits themselves could provide critical crosslinks as well [27••,58,59•,73••,74••].

Is the direct–indirect pathway model [75,76] of basal ganglia anatomy accurate? The concept that the subthalamic nucleus controls the release functions of the 'direct' basal ganglia pathway has been enormously influential in guiding new clinical treatments for Parkinson's disease and in interpreting basal ganglia functions (see [77,78•–80•,81••] and references therein). In this model, the basal ganglia can disinhibit the thalamus by way of a 'direct pathway' from striatum to the thalamus via the globus pallidus, pars interna (GPi) or SNr. Controlling or sculpting this disinhibition is the 'indirect pathway' from striatum to globus pallidus, pars externa (GPe) to subthalamic nucleus to GPi (and then to thalamus). Major clinical efforts have been mounted to use this information therapeutically in the treatment of Parkinson's disease: both lesions and stimulation of the subthalamic nucleus or the internal pallidum have been shown to relieve parkinsonian symptoms (see [76,81••,82] and references therein), apparently restoring a balance between the direct and indirect pathways that are lost in Parkinson's disease.

Parent and Hazrati [73••,74••] now question the existence of the indirect pathway: their anatomy in squirrel monkeys suggests that the subthalamic nucleus neurons receiving GPe input do not project to GPi, but, rather, back to GPe. They suggest that GPe should be considered as a general controller of a large set of nuclei including not only the GPi and SNr but also the thalamic reticular nucleus, a major modulator of thalamic function. The authors even suggest reserving the term 'indirect pathway' for projections from GPe to the internal pallidum (and SNr).

Anatomists are seldom at a loss to add 'new' pathways to a circuit diagram, but it is rare to find them subtracting one. If confirmed, the findings of Parent and Hazrati [73••,74••] will lead to considerable revision in thinking about phenomena ranging from clinical treatment protocols to differential regulation of neuropeptides in the basal ganglia, to current computational models based on the existence of direct and indirect pathways.

Revisions are also likely to result from other new information about the physiology and anatomy of the basal ganglia. Smith *et al.* [83••] report that the neocortical and thalamic inputs to the primate (squirrel monkey) striatum are strikingly different. First, corticostriatal terminals, but not thalamocortical terminals, can converge with nigrostriatal terminals on single spines in the primate striatum. Second, thalamic afferents to the striatum are reported to contact almost exclusively striatal neurons projecting to GPi, suggesting that the thalamus has a dominant control over the direct pathway (M Sidibé, Y Smith, *Neurosci Soc Abstr* 1994, 20:783). Tepper *et al.* [84••] report further evidence that collaterals of projection neurons in the SNr directly synapse on and inhibit dopaminergic nigral pars compacta neurons. This finding has major implications for basal ganglia functioning, including possible coordination of dopaminergic activity with activity of basal ganglia output pathways originating in the nigral complex. Findings such as these allow a glimpse of the variety and degree of specificity of the neural circuits associated with the basal ganglia.

What are the functions of striatal compartments? This question might have seemed esoteric a few years ago, but there is now dramatic evidence that striosomes, as defined histochemically by a variety of methods, are selectively vulnerable during the early stages of Huntington's disease. Hedreen and Folstein [85••] have proposed that the choreic movements of patients with Huntington's disease may partly be accounted for by this early loss. Striosomes are thought to innervate

preferentially the pars compacta of the substantia nigra, and loss of such (presumably inhibitory) input could, by changing functional activity in the nigrostriatal system, lead to the augmented movement patterns found in these patients. Interestingly, the only regions of the macaque monkey's frontal cortex so far found to project robustly to striosomes are in the posterior orbital cortex and the anterior cingulate cortex, regions that in humans have been implicated in obsessive–compulsive disorder [86•]. This finding has led to the suggestion that the anterior striosomal system may be particularly involved in the expression of such behavioral disorders and their normal behavioral counterparts [86•]. Striosomes have also been centrally implicated in reinforcement-based learning models of the basal ganglia [26••,57,87•,88•], following up an earlier hypothesis of White [89] that striosomes are part of a striatal reward system because they are preferentially linked to the limbic system. The anterior bias of this prefronto-striosomal system may contribute to the selective functions of the caudate nucleus in motor learning.

Evidence is accumulating that the matrix of the striatum is patchily organized (into matrisomes) as well, and that there are probably patterns of convergence, divergence and adjacency of corticostriatal inputs to matrisomes that set up templates for dynamically adjustable neural processing in the striatum (see [27••,58,86•]). Connolly and Burns [30•] have suggested that matrisomes correspond to state spaces in the striatum, which would fit well with the idea of matrisomes being critical to the adaptive functions of the basal ganglia [27••,30•,87•].

Conclusions

Integration of information across species, across brain regions and across levels of analysis is producing a new vigor in research on the basal ganglia. The articles reviewed here suggest that the basal ganglia are centrally concerned with the building up of adaptive behavioral action plans, and with the expression of these plans, under constraints imposed by forebrain and midbrain evaluator–reinforcement systems, through thalamocortical and brainstem executive systems.

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